Putting a Lid on Chemotherapy Costs

Genomic Health's Onco*type* DX Colon Cancer Assay assesses the risk of stage II colon cancer recurrence and potential adjuvant chemotherapy benefit. Cost savings could be huge.

BY BOB CARLSON, MHA, *Senior Correspondent*

Dr. Mehmet Oz doesn't smoke, eats a healthy diet, has no family history of colorectal cancer, is physically fit — and he's a favorite of Oprah. But none of that prevented a small adenomatous polyp from setting up house in Dr. Oz's colon.

The polyp was discovered last fall when CBS medical correspondent Jonathan D. LaPook, MD, did a colonoscopy on Oz and filmed it for broadcast on "The Dr. Oz Show." Benign adenomatous polyps in the colon can become cancerous, so LaPook, associate professor of clinical medicine at Columbia University, in New York, excised the polyp during the colonoscopy. This highly publicized event was a reminder that colon cancer can happen to anyone, even celebrity physicians.

"I worried about colon cancer about as much as being struck by lightning on a sunny day," Oz admitted in his column in the November 2010 issue of *Esquire*. In other words, this colonoscopy may have been a life saver.

When LaPook shared the news with Dr. Oz's audience, he pointed out that about 143,000 Americans are diagnosed with colon cancer annually, and about 51,000 will die from it. Colon cancer is the third most prevalent cancer in the United States and the third most common cause of cancer-related deaths.

But there's reason for optimism.

A recent advance in colon cancer treatment is the Onco*type* DX Colon Cancer Assay, developed by Genomic Health in Redwood City, Calif., and launched in January 2010. Highly regarded for its Onco*type* DX Breast Cancer Assay, the company developed this new multigene expression test to help physicians decide how to treat stage II colon cancer, which makes up approximately 30 percent of all colon cancers. Each year, 30,000 to 40,000 Americans are diagnosed with stage II colon cancer.

PHOTOGRAPH BY GARY WAGNER

"Clinical rigor and good science" underlie the Onco*type* DX Colon Cancer Assay, says Steven Shak, MD, Genomic Health's chief medical officer.

The stage II debate

Stage I colon cancer is confined to the inner wall of the colon and is cured by surgery alone in 95 percent of patients. Lymph nodes may harbor cancer cells in stage III colon cancer, where the risk of recurrence ranges from 30 percent to 80 percent, depending on the characteristics of the tumor. Adjuvant chemotherapy is the standard of care for stage III patients who are otherwise healthy. By definition, stage IV is metastatic disease and is treated with surgery and adjuvant chemotherapy, although a small percentage of patients also may be candidates for metastasectomy.

"That leaves stage II as the subset of colon cancer where the clinical management is not clear," says Michael J. O'Connell, MD, associate chairman of the National Surgical Adjuvant Breast and Bowel Project (NSABP) and professor of oncology

emeritus at the Mayo Clinic School of Medicine. "Stage II is really a debate, and if you look at the clinical practice guidelines, chemotherapy is recommended only for high-risk patients. The level of risk is what the Onco*type* DX Colon Cancer Assay tries to determine for patients, so we can make a more informed decision as to who should get chemotherapy and who shouldn't."

O'Connell's clinical expertise contributed to the design of the developmental studies for the Onco*type* assay to identify the important clinical questions the assay needed to address, as well as which clinical scenarios would be most relevant and the diagnostic markers that would maximize clinical utility of the test. O'Connell had observed the development of the Onco*type* DX Breast Cancer Assay, often in the same room with the principals, and lobbied for a similar test for colon cancer, a disease he had treated for 30 years as a medical oncologist at the Mayo Clinic.

"When we saw these fantastically significant *P* values correlating gene expression with outcome in breast cancer, my first thought was, 'We need to do this for colon cancer,'" says O'Connell, who is widely published and was on the board of directors for the Coalition of Cancer Cooperative Groups and a member of the National Cancer Institute Gastrointestinal Steering Committee. "I was very vocal with [Genomic Health Chief Medical Officer] Steve Shak and others to extend this technology to colon cancer."

The technology

The technology for the Onco*type* DX Colon Cancer Assay includes the microdissection of formalin-fixed, paraffin-embedded tumor tissue from which RNA is extracted and purified in a CLIA-certified, CAP-accredited reference laboratory. The RNA is analyzed using a technique called real-time reverse transcriptase-polymerase chain reaction (RT-PCR). An algorithm converts this quantitative gene expression analysis into a Recurrence Score from 0 to 100, which is included in a report for the ordering physician.

For this assay, the expression of each of seven cancer-related genes — Ki-67, C-MYC, MYBL2, FAP, BGN, INHBA, GADD45B — consistently associated with outcomes in colon cancer is measured and then normalized relative to five reference genes — ATP5E, PGK1, GPX1, UBB, VDAC2. These groups are representative of the two key biological pathways, cell cycle genes and stromal genes. Higher expression of cell cycle genes is associated with low recurrence score disease, low recurrence risk, and lower absolute benefit from chemotherapy. Higher expression of stromal genes is associated with high recurrence score disease, high recurrence risk, and greater absolute benefit from chemotherapy. All 12 genes were identified from an initial panel of 761 candidate genes in 1,851 patients with resected colon cancer in four development studies conducted by NSABP and the Cleveland Clinic Foundation in collaboration with Genomic Health.

"Cell cycle genes and stromal genes give us different information, but they complement each other," says Steven Shak, MD. Getting the right number of genes is important, Shak says. "Initially, we asked if fewer genes would do just as well, but, in fact, we lost information if we used fewer than 12 genes."

The Onco*type* DX Colon Cancer Assay involves a different biology and different genes than the Onco*type* DX Breast Cancer Assay, but the RT-PCR quantitative gene expression analysis method and the Genomic Health "approach" is common to both tests.

In addition to "clinical rigor" and "good science," Shak identifies three other components of the Genomic Health approach: Conduct the right studies that address the needs of patients, physicians, payers, and regulators; make the assay quantitative, reliable, and standardized — essentially the same principles that inform drug development; and engage leading experts who will collaborate in conducting studies and take the lead in presenting and publishing study results.

"It's not so much the money — you're sparing patients the side effects, inconvenience, and risks of adjuvant chemotherapy."– Michael J. O'Connell, MD

Cleveland Clinic biorepository

Genomic Health's widely adopted breast cancer assay attracted other colorectal cancer specialists like O'Connell, including a colorectal surgeon at the Cleveland Clinic, a colorectal cancer specialist at the University of Oxford in the United Kingdom, pathologists at the University of Leeds in the UK and the University of Pittsburgh, and biostatisticians at the University of Birmingham in the UK and the University of Pittsburgh.

"We started collecting frozen and fixed paraffin-embedded [colon cancer] tissue 20-plus years ago, not knowing exactly what we were going to do with it, but anticipating that there'd be molecular studies that would be developed," says Cleveland Clinic colorectal surgeon Ian Lavery, MD. "Because of our large, very good, complete database, we were naturally someone that Genomic

Health wanted to talk to when they were looking at the colon."

This biorepository of annotated colon cancer tissue specimens became an invaluable resource in the four developmental studies for the Onco*type* Colon Cancer Assay conducted by NSABP and the Cleveland Clinic Foundation. The tissue specimens for the Cleveland Clinic study came from patients whose colon cancer had been resected by Lavery and other Cleveland Clinic surgeons and who had been followed for more than five years postsurgery. After performing colorectal surgery for 35 years, Lavery is in a position to talk about the importance of removing lymph nodes adjacent to the cancer for pathologic examination.

"The American College of Pathologists has decided that 12 lymph nodes need to be examined before you can confidently say that it is a stage II tumor, not a stage III," says Lavery. If you remove six lymph nodes, and they're all clear, that's not adequate to say that it is a stage II tumor, Lavery explains. The more lymph nodes that are examined, the more likely it is that you'll find one or more that have metastatic disease in them. "At our institution, we remove a mean of 22 lymph nodes per colon resection."

The Onco*type* DX Colon Cancer Assay is being ordered by colorectal surgeons, gastroenterologists, and gastrointestinal (GI) oncologists. The recurrence score has been shown to add to the prognostic information available from traditional staging techniques (it's an independent prognostic variable in multivariate models), and the assay is used in combination with other prognostic information, such as the number of lymph nodes resected, microsatellite instability status, and T stage. Lavery has been using the assay for his stage II colon cancer patients since its launch in 2010. It's not definitive, he says, but "It's another tool to help us make a decision on whether a patient will benefit from chemotherapy after the surgery has been performed."

Peace of mind

Dominic (not his real name), a 44-year-old police sergeant in Ohio, became concerned enough about a persistent cough to see his family physician last summer. A physical examination, chest X-ray, and endoscopy showed nothing out of the ordinary, but blood work determined that Dominic was anemic, suggesting possible internal bleeding. A colonoscopy revealed a tumor in his ascending colon. Despite severe anemia and colon cancer, Dominic felt fine, other than occasional light-headedness after climbing stairs.

A relative who works at the Cleveland Clinic referred Dominic to colorectal surgeon Ian Lavery, MD, the same Ian Lavery who collaborated with Genomic Health in the development of the Onco*type* DX Colon Cancer Assay. After resecting Dominic's stage II tumor in August and excising 34 lymph nodes for pathological examination, Lavery explained the new test to Dominic. They agreed that it would make sense to order an Onco*type* DX Colon Cancer test on a sample of his tumor tissue.

"A couple of weeks later, he [Dr. Lavery] called me to his office and said that I scored a 13, which meant my risk of recurrence was low," Dominic says. "He said my tumor is a low-grade tumor and that chemotherapy would probably do more harm than good. He advised me to follow up with my family doctor and stay current with my colonoscopies. That was pretty much it."

The fact that it was his own tumor tissue that was being analyzed made a big difference for Dominic. "It's studying my cells," Dominic explains. "They weren't going to take a hundred people and say, well, the average stage II colon cancer is likely to recur 38 percent of the time. I knew it was specific for me, and that made me confident and gave me peace of mind."

QUASAR validation trial

Ideally, validation of an assay should be done by an independent third party that does not have access to data from the development studies. For the Onco*type* DX Colon Cancer Assay, that independent third party turned out to be a team of clinicians, biostatisticians, and pathologists in the UK led by principal investigator David Kerr, MD, DSci, FRCP, professor of cancer medicine at Oxford University and adjunct professor of medicine at Weill Cornell Medical College, in New York. Trained as a scientist and physician, Kerr specializes in the treatment and research of colorectal cancer, a topic on which he is widely published. He developed the "Kerr Report," a 20-year plan for the future of the National Health Service in Scotland. He is chief scientist for the new Sidra Medical and Research Center in Doha, Qatar, and practices in the Al Amal Cancer Hospital in Qatar, where he serves on the Supreme Council of Health. In 2010, Kerr was appointed president of the European Society of Medical Oncology and was also appointed Britain's health advisor.

"I saw the brilliant work Genomic Health had done in breast cancer, and I thought that it might be possible to replicate that in colon cancer, the tumor type in which I'm most in-

terested," says Kerr. "I contacted Steve Shak, we hit it off intellectually, and from those first phone calls came this important program of work. Colon cancer is the second commonest cancer in the western world. There's a large burden of disease."

Supported by the United Kingdom National Health Service, Kerr and his colleagues at Birmingham and Leeds conducted the validation trial using colon cancer tissue from 1,500 patients in the Quick and Simple and Reliable (QUASAR) clinical trial, which enrolled patients from 1994 to 2003 (QUASAR 2007). Tissue specimens were shipped to Genomic Health for testing, and the data were sent to Kerr's colleague in the UK, Richard Gray, who did the statistical analysis. The QUASAR study not only validated the Onco*type* assay, but was also the first study to show that chemotherapy is beneficial in treating stage II colon cancer.

"The patient data are entirely consistent between the NSABP studies in America and our studies," Kerr says. "The QUASAR study is 10 times bigger than any previous studies in colon cancer, and I think that's pretty compelling. It is the largest single trial ever undertaken for stage II colon cancer, and it was the first study to show that chemotherapy is beneficial. That was a major step forward. It was a large study, but a terribly important one and much quoted around the world."

Cost savings

The success of the validation trial led Kerr and colleagues in 2010 to embark on QUASAR 2, which randomizes stage II colon cancer patients to receive either standard chemotherapy using capecitabine or capecitabine plus bevacizumab (Avastin). "In QUASAR 2, we want to develop an assay to predict which patients will benefit from the addition of this expensive new drug," Kerr explains. "Rather than having to treat 100 patients to cure perhaps an extra two or three, it would be incredibly useful to have an RNA signature that predicted which patients might benefit. The cost savings would be huge." Study completion is expected in 2013.

Potential cost savings from the indicated use of the assay could also be huge. The list price for the Onco*type* DX Colon Cancer Assay is $3,200, while a typical course of chemotherapy can exceed $50,000 for one patient — a cost that could be avoided for every patient unlikely to benefit from chemotherapy.

"The cost of medical care needs to be considered in what becomes a standard of care and what we do for our patients," says O'Connell. Studies looking at the economic aspects of the Onco*type* recurrence score in the management of colorectal cancer, he says, suggest that the economic benefits outweigh the cost of the assay because you can identify patients that don't need chemotherapy, "and that saves millions of dollars in unnecessary treatment."

The Onco*type* DX Colon Cancer Assay is now available worldwide. That's a good thing, because the worldwide incidence of colon cancer is increasing as more people adopt a Western lifestyle. According to Kerr, epigenetic factors in the rising incidence of colon cancer include obesity, lack of exercise, too much red meat and not enough vegetables in the diet, smoking, and alcohol consumption.

Philip Agop Philip, MD, PhD, FRCP, sees the consequences of the Western lifestyle in his office every workday. Philip practices GI oncology and is professor of medicine and oncology at the Karmanos Cancer Center in Detroit. He first heard about the Onco*type* DX Colon Cancer Assay when Kerr presented the results of the QUASAR validation trial at the 2009 annual meeting of the American Society of Clinical Oncology (ASCO).

"My reaction was that in some patients this may be very helpful, because now I have some additional objective measures for making decisions regarding patients that have stage II disease," Philip recalls. "In the past, it was somewhat of a challenge to explain to patients who fall into the gray zone in stage II disease the pros and cons of treatment. Now, that process is easier."

After having ordered more than a dozen colon cancer assays, Philip says he wants to see improvement in the test's ability to discriminate between patients more likely and less likely to experience a recurrence of cancer. He also would like the test expanded to include patients with stage IIIa disease. Before the assay was launched, Philip says he was more likely than not to recommend adjuvant chemotherapy for stage II patients, just to be on the safe side. That's what many, if not most, GI oncologists and surgeons do. Philip adds that the assay's recurrence score may lead him to not only advise against chemotherapy, but also to recommend chemotherapy when it is appropriate.

The Onco*type* DX Colon Cancer Assay would not have been appropriate for Dr. Oz, but it's already making decisions about adjuvant treatment easier for physicians like Philip and for thousands of colon cancer patients.

Reference

QUASAR Collaborative Group, Gray R, Barnwell J, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomized study. *Lancet*. 2007;370:2020–2029.

Bob Carlson, MHA, writes exclusively about healthcare. He lives near Zionsville, Ind. Bob can be reached at bcarlson@biotechnologyhealthcare.com.